## REMARKS

The Examiner's office action dated December 9, 1994 has been carefully reviewed. Claims 1-4 and 6-21 are currently pending in this application. Claims 1-4 and 6-21 are subject to a restriction requirement and claims 6-21 have been withdrawn pending the filing of a divisional or continuation application. Claim 4 has been replaced by new claim 22.

The Rejection Under 35 U.S.C. §101

The Examiner has rejected claims 1-4 under 35 U.S.C. §101 as lacking patentable utility. This rejection is respectfully traversed.

The Examiner cites *Brenner v. Manson*, 383 U.S. 519, 148 USPQ 689 (1966) as establishing "that the utility of an invention may not based on **mere assertion**, but must rather be definite and in a currently available form." The Examiner has cited this case improperly. The issue was whether an application that had **no** assertion of utility was allowable under 35 U.S.C. §101.

The steroid compound that was made by the applicant's claimed process in *Brenner v. Manson* did not have any biological activity. It was not a steroid compound know to be produced or utilized in any biological organism. This is not true of the claimed cDNA to 4-1BB. 4-1BB is expressed in murine cells as part of the immune system. There is an inherent utility for a cDNA encoding a protein that is

involved in the murine immune system. 4-1BB is known to have biological activity in the immune system. The parent application filed 07/267,577 teaches that 4-1BB is a novel protein expressed differentially in T-cells

The Examiner is overly concerned about the function of 4-1BB *in-vivo*. The Examiner appears to be more concerned with how a mouse uses 4-1BB naturally, rather than how the claimed cDNA can be used by those skilled in the art. Such emphasis is inappropriate. The proper question is whether the applicant's have taught how one of ordinary skill in the art can put the invention to use.

Specifically, the applicant's teach that the claimed cDNA can be incorporated into an expression plasmid and the protein 4-1BB or a fusion protein can be expressed. Researchers can then test various compounds to see if the compounds affect 4-1BB expression or activity. If a compound showed such an effect it would be a concern with regard to use in humans unless such an affect on activity or expression was desired. Thus the claimed cDNA is a tool that allows researchers to directly test whether compounds affect the expression or activity or 4-1BB. Those compounds not intended to have an affect on the immune response, but that still affected 4-1BB expression or activity could be flagged as problematic.

The cDNA can also be used to make a fusion protein. The fusion protein is useful for finding ligand proteins for 4-1BB. The fusion protein is a tool that is useful in further characterizing the immune system. These tools are useful in the same way that a microscope is useful in learning more about a bacterium. The fact that a product can be used in research does not mean that it has no utility.

The Applicant's have alleged that the cDNA can be used to create a recombinant protein which can be used to create a mAb to 4-1BB. This mAb has been shown to include cross-linking in T-cells and therefore enhance T-cell activation and proliferation. This product has usefulness in culturing of T-cells as well as therapeutic uses. Cross-linking is necessary for the successful culturing of T-cells. The Examiner responds to this by stating that the mAb is a patentably distinct invention. The relevance of the Examiner's statement is not understood. The fact that the claimed cDNA can be used to make another patentable product seems to support the utility of the claimed cDNA rather than refute it. Furthermore, the Examiner states that:

> "the Applicant's suggestion that the claimed 4-1BB cDNA sequence can be used to make the 4-1BB protein which in turn can be used to immunize mice to make monoclonal antibodies which then can be used to enhance the proliferation of anti-CD3-stimulated T cells is a bit strained."

The Examiner does not state any objective evidence to support her conclusion that the Applicant's arguments are "strained". Does the Examiner question whether the mAb (53A2) deposited with ATCC actually works, or that the applicant actually observed T-cell activation and proliferation when conducting the experiments? The disclosure describes these experiments in great detail. The Examiner states that the applicant "failed to specify the type of cell cultures or what effect the monoclonal antibody will have on cultured cells." The applicant clearly describes that for anti-CD3 stimulated T-cells, the mAb will enhance activation and proliferation. The specification also suggests a role for 4-1BB *in vivo*, however, as stated above, the

whether or not 4-1BB is an accessory signaling molecule *in vivo* does not change the fact the those skilled in the can use the mAb to enhance the activation and proliferation of T-cells *in-vitro* which is useful as a reagent in the culturing of T-cells.

With regard to the use of the claimed cDNA in therapy, the Examiner states: "presumably appellant (and the specification are referring to the application of the suppression of B cell proliferation in human organ transplants, and not mice." Why has the Examiner made this presumption? The entire specification refers to mice. The claimed cDNA encodes murine 4-1BB not human 4-1BB. Specifically, 4-1BB expressing SF-21 cells were used to stimulate resting murine B cells. Mice are extensively used as a model for humans and much research for therapy is performed in mice prior to humans. For example, the "Harvard Mouse" had a great deal of commercial value because of its ability to act a model for testing human compounds. Because of the extensive use of mice for this purpose a great deal of research and tools have been developed for use with mice. Furthermore, there is no requirement that a product have commercial utility, but merely that it is capable of some useful purpose other than solely research. So while the Examiner may not see the commercial utility of stimulating resting murine B cells, it does not mean that such methods do not have patentable utility. Applicant's do not need to demonstrate a human therapy for purposes of 35 U.S.C. §101.

The Examiner states that on page 80, lines 23-27, the specification teaches that the effect of 4-1BB on B cells is unknown. These statements merely indicate the plans for further research with regard to the *in vivo* role of 4-1BB, but do not change the teaching of the specification that one skilled in the art can use SF-21 expressing 4-1BB

with resting B cells to induce proliferation. The fact that there is more to know or discover does not mean that which is already known is not true. The applicants have shown a method of using of the claimed cDNA to induce B cell proliferation and teach that use of a fusion protein or an antibody that binds to 4-1BB or its ligand could block this interaction and therefore suppress B-cell proliferation. It is not necessary for the applicant to know all uses of a particular product for there to be patentable utility.

The Examiner's statements are not supported by any objective evidence contradicting the teachings of the specification. *In re Langer*, 503 F.2d 1380, 1391 (CCPA 1974) states:

> "a specification which contains a disclosure of utility which corresponds in scope to the subject matter sought to be patented must be taken as sufficient to satisfy the utility requirements of §101 for the entire claimed subject matter unless there is reason to question the objective truth of the statement of utility or its scope."

The Examiner has not stated any reason to question the objective truth of the applicant's allegations of utility. Once an assertion of utility is made the Examiner can only rebut the assertion with objective evidence. The Examiner conclusory statements are insufficient.

The specification alleges numerous uses of the claimed cDNA. The Examiner does not present any objective evidence to refute the allegations of utility. The Examiner's argument that all of the uses of 4-1BB cDNA are not known or that all information about the *in-vivo* role of 4-1BB is not know are not relevant for

considering patentable utility. The current and parent applications allege a "definite and currently available utility" for the claimed invention. Therefore, the reconsideration and withdrawal of this rejection is respectfully requested.

The Rejection Under 35 U.S.C. §112

The Examiner has rejected claims 1-4 under 35 U.S.C. §112. This rejection is respectfully traversed.

First, with respect to claim 4, replaced by claim 22. The new claim is believed to satisfy the objections of the Examiner that were unique to claim 4. Specifically, new claim 22 recites a DNA that encodes an amino acid shown in Figures 2a and 2b and probes that could be used to isolate such a sequence. Thus the claimed DNA is readily identifiable by all those skilled in the art and examples of a sequence and probes are taught in Figures 2a and 2b and on page 17, lines 26-31.

The Examiner states that the applications fails to teach how to use the cDNA recited in claims 1-4. The Examiner states that "one skilled in the art must know which ligand binds to the receptor in order to use it." The Examiner does not provide any objective evidence to support such a statement. The specification specifically teaches methods of using the claimed cDNA to isolate or make similar sequences, recombinant proteins, fusion proteins, mAb's that enhance T-cell proliferation and activation, and SF-21 4-1BB expressing cells that can be used to induce B-cell proliferation. The specification describes in detail the methods and materials to use

the claimed cDNA to accomplish these ends. The utility of such products and methods is discussed above.

Claims 1-3 and 22 are believed to be allowable under 35 U.S.C. §112 and the Examiner's reconsideration and withdrawal of this rejection is requested.

The Denial of the Benefit of the Filing Date of Prior Application and Rejection Under 35 U.S.C §102

The Examiner stated that the claimed invention is denied the benefit of the filing date of the prior applications as the prior applications do not contain an adequate written description. After denying the benefit of the earlier filing date, the Examiner rejected claims 1-4 over the applicant's publication which discloses less than the parent application. This denial of priority and rejection are respectfully traversed.

Application Serial No. 07/267,577, filed November 7, 1988 disclosed the sequence of the claimed cDNA and refers to a deposit of the cDNA. The specification also taught how to use the cDNA to make a recombinant protein and to isolate the human homologue for 4-1BB. Both the sequence information and the deposit have long been held to satisfy the enablement requirements f the 35 U.S.C. §112 and the Examiner's position is directly contradictory to long-standing case law. The Examiner states that:

> "The parent application 07/267,577 teaches that 4-1BB is a novel sequence of unknown function. Note p. 2, lines 40-42. In addition, in

contrast to the instant application which teaches that 4-1BB is a protein receptor, the parent application suggests that instant cDNA sequence encodes a **lymphokine**, a soluble the protein secreted by a lymphokine."

The Examiner's statements are incorrect. First, the section of text the Examiner refers to merely states that unlike the other transcripts isolated using the novel differential screening technique, isolates 4-1BB and L2G25B were novel sequences that had previously not been characterized. Following, this description is a detailed characterization of the sequences. Secondly, the parent application teaches that "the deduced amino acids of 4-1BB has characteristics of the signal peptide of secretory and membrane-associated protein" (See page 13, lines 7-9). Furthermore, the present specification also teaches that 4-1BB may also have a secreted form (See page 80, lines 17-19 of present application) The line between receptor protein and lymphokine is not as clear as the Examiner suggests. Other proteins are both secreted and expressed on the cell surface. (See page 80, lines 15-22 of present application.) The current application definitely teaches that 4-1BB is expressed on the cell surface, but the teachings of the parent application and the characterization of 4-1BB as a novel protein involved in the immune system and expressed differentially in T-cells are also accurate and one skilled in the art was enabled to make and use the claimed invention at the time of filing of the parent application.

Furthermore, this denial does not make sense in view of the art rejections relying upon Kwon *et al.* (1989). This reference teaches far less than the parent application yet the Examiner relies upon for the art rejection. If the application fails to meet the requirements for enablement, how can the reference be sufficiently